REVIEW ARTICLE

Real-world Challenges and Predictors of Success in Glucagon-like Peptide-1 Receptor Agonist Therapy

Nitin Mohaniraj Patankar[1*], Sushma Jain Sanghvi [2]

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Abstract

Background: Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have revolutionized the management of type 2 diabetes mellitus (T2DM) and obesity, demonstrating robust efficacy in landmark trials for glycemic control, weight reduction, and cardiovascular protection. However, real-world discontinuation rates exceed trial-reported rates, highlighting a gap between clinical efficacy and practical outcomes.

Objective: This review synthesizes evidence from 2018 to 2024, including trial data, population studies, and registry analyses, to identify and contextualize major real-world barriers. High rates of gastrointestinal side effects, substantial out-of-pocket costs, and patient aversion to injectable formulations often result in 1-year discontinuation rates ranging from 27 to 41%. These challenges are compounded by heterogeneity in patient response, with predictors of successful long-term use including higher baseline HbA1c, elevated body mass index (BMI), absence of severe gastrointestinal disorders, and robust early response to therapy.

Methods: A proposed clinical scoring model is presented to improve patient selection and predict adherence, while digital health tools and emerging combination therapies offer additional avenues to enhance persistence and outcomes. Despite promising advances such as dual- and triple-incretin agents and oral GLP-1 RA formulations, cost and access remain major hurdles.

Results: Key factors, including baseline HbA1c >8.0%, BMI >30 kg/m^2, absence of severe gastrointestinal (GI) disorders, and prior adherence success, correlate strongly with higher persistence. Real-world data reveal that discontinuation rates for GLP-1 receptor agonists remain high, with 1-year discontinuation ranging from approximately 28% to around 41%, depending on the patient population and indication. Discontinuation is more common among patients using GLP-1 RAs for obesity without diabetes, reaching rates above 50% in some cohorts. The primary reasons for stopping therapy include gastrointestinal side effects, reported in over 25% of discontinuations, high medication costs, and issues with insurance coverage or medication access. Persistence is generally higher among patients with T2DM, those with higher baseline BMI, and those who experience greater early weight loss or favorable tolerability, while frequent adverse effects and logistical barriers contribute to poorer long-term adherence. Although emerging clinical tools and digital health interventions are proposed to help address these barriers, further prospective data are needed to quantify their impact on persistence at scale.

Conclusion: Bridging trial evidence with real-world practice requires proactive candidate profiling and side-effect management. Combining predictive scoring, artificial intelligence (AI)-supported adherence tools, and emerging dual-incretin agents may transform GLP-1 RA therapy from short-term use to durable metabolic benefit.

Keywords: Glucagon-like peptide-1 receptor agonists, Glycated hemoglobin, Obesity, Predictive success, Type 2 diabetes mellitus.

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Introduction: The Promise and Challenges of Glucagon-like Peptide-1 Receptor Agonists

Type 2 diabetes mellitus (T2DM) and obesity are major global health concerns, with their prevalence continuing to rise despite advances in therapeutic options. Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) have emerged as a cornerstone in the management of these conditions, offering benefits that extend beyond glycemic control to include significant weight loss and cardiovascular protection. Drugs such as semaglutide, liraglutide, and dulaglutide have demonstrated efficacy in landmark clinical trials such as LEADER, SUSTAIN, and AWARD-7, reinforcing their role in reducing major adverse cardiovascular events and improving metabolic health.[1,2]

Despite their strong evidence base, translating these benefits from controlled clinical trials to real-world practice presents substantial challenges. Discontinuation rates for GLP-1 RAs is consistently higher than trial dropout rates, because of a combination of gastrointestinal side effects, high costs, and patient reluctance toward injectable formulations.[3–5] Additionally, variability in patient response, driven by factors such as baseline glycemic control, visceral adiposity, and comorbid conditions, further complicates their widespread adoption.

This review critically examines the real-world challenges of GLP-1 RA therapy, proposes a predictive framework for identifying ideal candidates, and explores emerging solutions, including the integration of digital health tools and novel combination therapies. By addressing these limitations, health care providers can enhance adherence, improve long-term outcomes, and ensure more effective utilization of these potent therapies.

Challenges in Real-world Glucagon-like Peptide-1 Receptor Agonists

While GLP-1 RAs have demonstrated significant efficacy in clinical trials, their real-world application is hindered by several challenges. These issues span patient adherence, drug tolerability, financial accessibility, and the presence of comorbid conditions that may limit eligibility. Understanding and addressing these barriers are critical to optimizing the long-term success of GLP-1 RA therapy.

Adherence and Persistence: The Dropout Problem

Adherence to GLP-1 RAs in real-world settings is significantly lower than in clinical trials. Studies report discontinuation rates of up to 28% within 6 months and poor 1-year persistence, with only 59% of patients continuing therapy.[3,6] The main reasons for this include:

Gastrointestinal side effects: Nausea, vomiting, and diarrhea are the most common

[1]Consultant, Department of Diabetes and Bariatric Medicine, Jupiter Hospital, Thane; [2]Consultant, Department of Metabolic Centre, Dr L H Hiranandani Hospital, Mumbai, Maharashtra, India; *Corresponding Author

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adverse events, occurring in 20–30% of patients and often leading to premature discontinuation.[4,7]

Cost and insurance coverage: GLP-1 RAs are expensive, with out-of-pocket costs acting as a major deterrent. A cost-effectiveness analysis indicated that oral semaglutide was unlikely to be cost-effective unless prices were significantly reduced.[5] Insurers remain hesitant to cover these medications, especially for obesity treatment alone.

Injection aversion: Despite the availability of oral semaglutide, many patients remain reluctant to start or continue injectable GLP-1 RAs.

Dosing frequency: Weekly formulations such as semaglutide and dulaglutide show better adherence compared with daily regimens, with 12-month persistence rates of approximately 55–60%.[3]

Addressing these issues requires patient education, gradual dose titration, and the use of digital health tools to track adherence and reinforce treatment benefits.

Tolerability Issues: Managing Side Effects to Improve Persistence

The most frequently reported side effects, nausea, vomiting, diarrhea, and abdominal pain, are linked to GLP-1 receptor activation in the gastrointestinal tract, leading to delayed gastric emptying.[4,7] Strategies to improve tolerability include:

Gradual dose escalation: Starting with a lower dose and titrating upward over 4–8 weeks significantly reduces gastrointestinal side effects.[7]

Proactive patient education: Patients who are informed about expected side effects and management strategies (e.g., taking the medication with food and avoiding large meals) are less likely to discontinue treatment prematurely.

Individualized therapy selection: Patients with a history of gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), or gastroparesis are at a higher risk of experiencing intolerable gastrointestinal (GI) symptoms and may not be ideal candidates for GLP-1 RAs.[7]

Patient Selection: Who Benefits the Most?

The response to GLP-1 RA therapy is not uniform across all patients. Studies suggest that outcomes are influenced by baseline metabolic characteristics, including:

Baseline HbA1c: Higher HbA1c levels (>8.0%) predict greater glycemic benefit from GLP-1 RAs.

Body mass index (BMI): Patients with BMI >30 kg/m^2 tend to have a more pronounced weight loss response, making them ideal candidates for this therapy.

Visceral adiposity: Patients with central obesity often experience better metabolic outcomes than those with peripheral adiposity.

Comorbidities: The presence of advanced chronic kidney disease (CKD) or severe gastrointestinal disorders may limit therapy options.[2]

The AWARD-7 trial demonstrated dulaglutide's renal benefits in patients with diabetes and CKD, making it a preferred option in this subgroup.[2] However, patients with gastroparesis, GERD, or IBS face a higher risk of symptom exacerbation and therapy discontinuation.

Predicting Success in Glucagon-like Peptide-1 Receptor Agonists Therapy–A Scoring Model for Clinical Decision-making

Given the variability in patient response, a predictive framework can help clinicians identify ideal candidates for GLP-1 RA therapy and mitigate risks associated with discontinuation. The proposed scoring system in Table 1 incorporates metabolic, psychological, and gastrointestinal factors to estimate treatment success.

Interpretation

Score ≥7 → High likelihood of successful therapy. Strong candidate for GLP-1 RA therapy.

Score 4–6 → Moderate benefit expected. Requires patient education and close monitoring for side effects.

Score 0–3 → Low likelihood of success. Alternative therapies should be considered.

Score ≤–1 → High risk of adverse effects and treatment failure. Strong recommendation for alternative treatment strategies.

Strengthening the Predictive Model with Real-world Evidence

While the above framework is based on clinical experience and trial data, its real-world application needs further validation through observational studies. Potential areas for improvement include:

Longitudinal tracking of patients to assess real-world persistence beyond 6 months.

Digital health integration, using artificial intelligence (AI)-driven models to refine predictions based on patient adherence data.[9]

Incorporating genetic and gut microbiome profiling, which may provide additional insights into therapy responsiveness.

The Role of Digital Health in Enhancing Glucagon-like Peptide-1 Receptor Agonists Therapy

Emerging evidence supports the use of digital health tools to improve adherence and treatment outcomes. These include:

Real-time glucose monitoring [continuous glucose monitoring (CGM)]—Helps track glycemic trends and ensures early intervention.

AI-driven patient support apps (MySugr, Carb Manager)—Provide tailored dietary and lifestyle recommendations.

Telemedicine and virtual coaching—Address patient concerns, encourage

Table 1: GLP-1 RA therapy success score

Factor	*Score (–2 to +2)*	*Rationale*
Baseline HbA1c >8.0%	+2	Greater glycemic improvement potential
BMI >30 kg/m^2	+2	Stronger weight loss benefits, better metabolic outcomes
Visceral adiposity presence	+1	Correlates with enhanced response to GLP-1 RAs
No prior GLP-1 RA failure	+1	Higher adherence likelihood if no past discontinuation due to intolerance
No severe GI disorders (GERD, IBS, gastroparesis)	+2	Lower dropout risk due to GI side effects[7]
No history of eating disorders	+1	Reduces psychological barriers to adherence[8]
No severe anxiety/depression	+1	Improved adherence and persistence[8]
History of severe GI disorders	–2	Increased risk of treatment discontinuation
History of eating disorders	–1	Increased risk of poor adherence and negative psychological impact
Severe depression or anxiety	–2	Higher risk of therapy discontinuation[8]

adherence, and enable dose titration without frequent clinic visits.

Bio-wearables—Devices such as Fitbit and Apple Watch monitor metabolic parameters to assess therapy effectiveness.[9]

By integrating predictive models with digital health, clinicians can proactively adjust treatment plans and ensure better long-term success for GLP-1 RA therapy.

Future Directions and Conclusion

Emerging Therapies: The Next Generation of Glucagon-like Peptide-1-based Treatments

While GLP-1 RAs have proven highly effective, the next wave of metabolic treatments is poised to further enhance efficacy, tolerability, and accessibility.

Dual- and Triple-Incretin Therapies

Tirzepatide [glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA]: Clinical trials suggest greater HbA1c and weight reduction than semaglutide, making it a promising alternative.[10]

GLP-1/GIP/glucagon RAs: Early research indicates that adding glucagon receptor activity may improve energy expenditure and fat metabolism, potentially overcoming weight-loss plateaus.

Oral and Long-acting Injectable Formulations

Oral semaglutide: Despite improving adherence in injection-averse patients, its cost-effectiveness remains a concern.[5]

Ultra-long-acting GLP-1 RAs: Agents with biweekly or monthly dosing could enhance persistence and reduce dropout rates.

Personalized and Precision Medicine Approaches

Pharmacogenomics and microbiome research may help predict which patients respond best to GLP-1 therapy.

Artificial intelligence (AI) integration can optimize dosing schedules based on real-time metabolic data.[9]

Cost-effectiveness and Healthcare System Implications

The widespread adoption of GLP-1 RAs is hindered by cost considerations, particularly in regions where insurance coverage is limited. Economic analyses suggest:

Cost per quality-adjusted life year (QALY): GLP-1 RAs become cost-effective when reducing hospitalization rates and cardiovascular events.[11]

Comparative cost-effectiveness: Tirzepatide's enhanced efficacy may justify its cost premium over semaglutide.[12]

Health policy impact: Expanding insurance coverage and negotiating drug prices are crucial for improving access to these life-changing therapies.

Key Takeaways: Translating Clinical Success into Real-world Impact

To maximize the success of GLP-1 RA therapy in routine practice, the following strategies must be prioritized:

Optimized patient selection—Using predictive models to ensure that the right patients receive GLP-1 RAs, improving outcomes and cost-effectiveness.

Proactive side effect management—Employing dose-titration protocols and patient education to mitigate nausea and discontinuation rates.

Integration of digital health tools—Leveraging real-time glucose monitoring, AI-driven coaching, and telemedicine to enhance adherence.

Emerging therapies and personalized medicine—Preparing for the future of multi-incretin therapy and utilizing genetic and metabolic profiling to personalize treatments.

Addressing cost barriers—Advocating for insurance reimbursement policies and alternative pricing models to improve affordability.

Conclusion

GLP-1 RAs represent one of the most transformative developments in the management of T2DM and obesity, offering unparalleled benefits in glycemic control, weight loss, and cardiovascular protection. However, real-world challenges such as high discontinuation rates, tolerability concerns, and cost barriers necessitate a comprehensive, patient-centered approach.

By integrating predictive scoring models, digital health interventions, emerging combination therapies, and policy-driven affordability strategies, health care providers can optimize treatment success and ensure that GLP-1 RAs fulfill their potential as a cornerstone therapy for metabolic disease.

Orcid

Nitin Mohaniraj Patankar https://orcid.org/0009-0006-9076-9770
Sushma Jain Sanghvi https://orcid.org/0009-0006-5763-0021

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